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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,998	01/04/2001	Ernst H. Rinderknecht	P0941C1D1C1	4682

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/15/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/754,998	Applicant(s) RINDERKNECHT ET AL	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-31* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 19-26 have been canceled.

Claim 27 has been amended.

Claims 30-31 have been added.

2. Claim 29 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

3. Claims 27-28 and 30-31 are under examination with the elected species Her2.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 19-26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

7. The rejection of claims 19-20, 23-28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-10 of U.S. Patent No. 6,066,719 is withdrawn in view of the filing of a terminal disclaimer.

8. The rejection of claims 19-25 under 35 U.S.C. 102(e) as being anticipated by Carter et al (U.S. Patent 6,054,297, filed 5/95 and is a CON filed 8/92) is withdrawn in view of the amendments to the claims.

9. The rejection of claims 19, 21, and 23 under 35 U.S.C. 102(b) as being anticipated by Hudziak et al (WO 89/06692, published 7/89) is withdrawn in view of the amendments to the claims.

10. The rejection of claims 19-26 under 35 U.S.C. 103(a) as being unpatentable over Carter et al (U. S. Patent 6,054,297, filed 5/95 with priority as a CON to 8/92) as applied to claims 19-25 above, and further in view of Morimoto et al (J. Biochem. Biophys. Methods 24:107-17, 1992, IDS #4.5) is withdrawn in view of the amendments to the claims.

11. The rejection of claims 19-26 under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al (WO 89/06692, published 7/89) as applied to claim19, 21, 23 above, and further in view of Morimoto et al (J. Biochem. Biophys. Methods 24:107-17, 1992, IDS #4.5) is withdrawn in view of the amendments to the claims.

Response to Arguments

12. The rejection of claims 27-28 under 35 U.S.C. 103(a) as being unpatentable over Carter et al (U. S. Patent 6,054,297, filed 5/95 with priority as a CON to 8/92) and further in view of Morimoto et al (J. Biochem. Biophys. Methods 24:107-17, 1992, IDS #4.5) is maintained.

The response filed 2/28/03 has been carefully considured but is deemed not to be persuasive. The response states that Morimoto et al fails to discuss the problem of the presence of incorrectly disulfide linked antibody fragments in a recombinant antibody and Morimoto et al is also deficient in describing a composition wherein such a contaminant has been removed (see page 6 of response) and the antibody fragments weren't recombinantly produced and Morimoto used pH 7.4 which would result in incorrectly disulfide antibodies being greater than claimed (see page 7 of response). In response to these arguments, the rejected claims recite nothing about incorrect disulfide linked antibody fragments, therefore Morimoto et al does not have to identify this. In addition, the recitation of "recombinant" in newly amended claim 27 indicates how the antibody is produced and is therefore a product by process. The method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113. Thus, the art of Morimoto et al reads on the claim because the term "recombinant" is given no patentable weight as a product by process.

13. The rejection of claims 27-28 under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al (WO 89/06692, published 7/89) and further in view of Morimoto et al (J. Biochem. Biophys. Methods 24:107-17, 1992, IDS #4.5) is maintained.

The response filed 2/28/03 has been carefully considured but is deemed not to be persuasive. The response states the same arguments as those above and as such the same response applies.

The following are some NEW GROUNDS of rejection

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Morimoto et al (J. Biochem. Biophys. Methods 24:107-17, 1992, IDS #4.5).

The claim has been described supra.

Morimoto et al teach a F(ab')2 fragment purified to greater than 98% in a composition comprising PBS.

The response filed 2/28/03 has been carefully considured but is deemed not to be persuasive. The response states that Morimoto et al fails to discuss the problem of

the presence of incorrectly disulfide linked antibody fragments in a recombinant antibody and Morimoto et al is also deficient in describing a composition wherein such a contaminant has been removed (see page 6 of response) and the antibody fragments weren't recombinantly produced and Morimoto used pH 7.4 which would result in incorrectly disulfide antibodies being greater than claimed (see page 7 of response). In response to these arguments, the rejected claims recite nothing about incorrect disulfide linked antibody fragments, therefore Morimoto et al does not have to identify this. In addition, the recitation of "recombinant" in newly amended claim 27 indicates how the antibody is produced and is therefore a product by process. The method in which the antibodies were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113. Thus, the art of Morimoto et al reads on the claim because the term "recombinant" is given no patentable weight as a product by process.

16. Claims 27 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Neblock et al (Bioconjugate Chem. 3:126-131, 1992, IDS #4 ½) .

The claims recite a composition comprising a correctly disulfide linked recombinant F(ab')2 wherein the F(ab')2 is at least about 95% and a mixture of

incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment wherein the purity of the correctly disulfide linked antibody fragment is at least about 95% and the fragment is a F(ab')2 and the composition comprises a physiologically acceptable carrier.

Neblock et al teach compositions comprising bispecific F(ab')2 fragments that are 93% pure and compositions in phosphate buffer (see Experimental procedures and page 128-129, production of Bispecific F(ab')2). Neblock et al teach that the composition comprises F(ab')2 and Fab' (see Figure 3 and text at page 129). The phrase incorrectly disulfide linked is being interpreted to be the free Fab' or reduction of H-L chains (see page 128, left column) which is not the correct product and therefore the art reads on the claim.

Claim Rejections - 35 USC § 103

17. Claims 27-28 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neblock et al (Bioconjugate Chem. 3:126-131, 1992, IDS #4 ½) as applied to claims 27 and 30-31 above and further in view of Shalaby et al (J. Exp. Med 175:217-225, 1992).

The claims recite a composition comprising a recombinant correctly disulfide linked antibody fragment at least about 95% purity and a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment wherein the purity of the correctly disulfide linked antibody fragment is at least about 95% and the

fragment is a F(ab')2 and the composition comprises a physiologically acceptable carrier and the antibody binds HER2.

Neblock et al teach compositions comprising bispecific F(ab')2 fragments that are 93% pure and compositions in phosphate buffer (see Experimental procedures and page 128-129, production of Bispecific F(ab')2). Neblock et al teach that the composition comprises F(ab')2 and Fab' (see Figure 3 and text at page 129). The phrase incorrectly disulfide linked is being interpreted to be the free Fab' or reduction of H-L chains (see page 128, left column) which is not the correct product. Neblock et al does not teach a bispecific antibody with Her2. This deficiency is made up for in the teachings of Shalaby et al.

Shalaby et al teach production of bispecific antibodies that bind Her2

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a bispecific antibody with specificity to Her2 wherein the composition comprises the bispecific antibody at 93% purity in the composition.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a bispecific antibody with specificity to Her2 wherein the composition comprises the bispecific antibody at 93% purity in the composition because Neblock et al teach the bispecific antibody is 93% pure and Neblock et al teach that the composition comprises F(ab')2 and Fab' (see Figure 3 and text at page 129). The phrase incorrectly disulfide linked is being interpreted to be the free Fab' or reduction of H-L chains (see page 128, left column)

which is not the correct product. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a bispecific antibody with specificity to Her2 wherein the composition comprises the bispecific antibody at 93% purity in the composition because Shalaby et la teach that the bispecific antibody that binds Her2 is effective in targeting tumor cells (see page 218). It would have been obvious to produce the bispecific antibody of Shalaby with the method of Neblock et al because the crosslinked antibody is stable and nonreducible (see page 129 and page 130, right column).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879